A PRELIMINARY REPORT OF THE POSSIBLE RELATIONSHIP OF NEURO-FIBRILLAR CHANGES TO INSANITY.[1]

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As Nissl states, it is necessary in order to have a pathology of the nerve cell that there be a well defined anatomy of the cell. The neurologist is at present engaged in studying the relationship of cells and the tracts of their processes.

To the psychiater it would seem that the morphology and physiology of the individual cell were the principal things to be studied; for it is from the structure and function of the nerve cell and its processes that we hope to learn something of the relation of mind to the physical process.

The value of becoming conversant with the morphological relations existing inside the nerve cells is without question, when we think of being able to trace a bearing on function in the capacity they exhibit for responding to external irritation and of storing up and reproducing happenings which go on outside of the cell.

During the past summer, in the laboratory of Friends' Asylum, we have been studying changes in neuro-fibrils as shown by the method of Cajal, published in the *Compt. rend, de la Soc. de Biol.,* Dec. 18, 1903, with a view of determining the possible relationship of changes in fibrils to insanity.

As far back as 1844 Remak[2] called attention to a fibrillary structure in certain axis cylinders and nerve cells.

Max Schultze followed with notable researches, in which he demonstrated that fibrils are seen in all parts of the cell and also in the dendrites as well as in the axone.

He said that the nucleus lay imbedded in the finely granular fibrillated material, but did not have any connection with the fibrils.

Then, in 1885, Nissl described the granular bodies which bear his name, which Rosin thinks should be considered in their chemical nature rather than morphologically; Benda having seen this same appearance in glands and Cajal in leucocytes and connective tissue. Macallum showed that there was iron in these bodies. While Haliburton distinguished a nucleo-albumin containing phosphorus; and from the quantity of work which has been done by investigators we must accept the suggestion that they are an index to the internal metabolism of the cell. These observations and the chemical experiments of Held and others tend to throw the burden of evidence of conduction on the achromatic substance.

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[1] Read at the meeting of the Philadelphia Neurological Society, October 25. 1904.

[2] Barker, "The Nervous System."

The majority of investigators also seem to be agreed that the achromatic or non-stainable portion of the cell body is closely allied, if not identical, with that of the axone. Certainly the fibrils are in the non-stainable portion (in the sense of Nissl) of the cell.

Apáthy in describing his nerve cell states that it produces neurofibrillæ just as a muscle cell produces muscle fibrillæ. He also compares nerve cells with muscle cells in their histogenesis, and believes that a nerve cell is no more capable of the highest functions of conduction before the appearance of the neurofibrillæ than is a muscle cell of the highest functions of contraction before its peculiar fibrillæ have been differentiated. The stain of Apáthy, however, has not been of value when applied to the nervous system of higher mammals. Apáthy claims that the neuro-fibrils in the lower animals represent the essential element of conduction. Bethe[3] shares this view.

Held looks upon the ground substance as a whole, as a means of propagation of stimuli.

Leydig[4] attributes conduction to the plasma which fills the meshes of the cellular network.

Others say it is the spongioplasm.

Butschli considers the frame work of the nerve cell protoplasm the histological basis of conduction. The opinions on these points are various.

Considering the fibrils as demonstrated in the peripheral nerves by Bethe's method with osmic acid, he states that where the nerve has been well stretched we see the fibrils in straight lines and individually separated, lying side by side, without any connection at all, until they bifurcate to branch off, and that they never end except when cut by the knife. Consequently he regards them as real individual fibrillæ, and of circular form. He further says that there is no difference between the neuro-fibrillæ of the efferent and afferent fibers; and that when in the Ranvier's nodes, the fibrils are kept at certain distances from each other, and this can be explained as an insulating function, the insulating substance preventing the contact of the threads.

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[3] Bethe, Alleg. Anat. und Phy. des "Nervensystem."

[4] Leydig, Archi. für Anat. and Physio., 1897.

After many experiments of pressure on the nerves he arrived at the conclusion that the perifibrillar substance is completely interrupted in the Ranvier's nodes, and only the neuro-fibrillæ pass continuously and uninterruptedly from one medullary partition to another. This being the case the fibrillæ are the conductors of the nerves.

In 1896 Lugaro[5] formulated an important generalization with regard to the respective significance of lesions of the chromatic and achromatic parts of the cytoplasm. He maintained that alterations to the chromatic parts do not represent more than a reaction of the cell to a disturbing force and are reparable; while on the other hand, alterations of the achromatic parts are to be regarded as degenerative and irreparable. From experimental pyrexia and poisoning, some observers are led to maintain that chromatolysis has little significance as a pathological change; for cells showing many changes had still been able to perform their functions, and it has thus been argued that the Nissl bodies can have no marked importance in functional activity. Lugaro, however, holds that while the activity does continue, yet it is less in degree, and that the chromatic part fulfils its functions through its chemical and not its morphological structure. He thinks the morphological conditions necessary to function consist in the structure of the achromatic substance, and the intensity of function depends on the chromatic.

If this view be true there could be considerable mental weakening due to chromatic chemical changes before there would be noted any marked change in achromatic substance.

In poisoning by ether or chloroform there may be no demonstrable lesion, while, even after functional disturbances have disappeared after compression of the abdominal aorta, the lesion of the chromatic parts is present.

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[5] Lugaro, Riv. di patol. nerv. e ment, 1896 and 1898.

But we can hardly doubt that the chromatic part plays a very important rôle in the functional metabolism of the nervous element and that its alterations are an index of a nutritive change.

Marinesco and Robertson[6] agree that yellow pigment is an evidence of senile involution, and with the formation of pigment there is usually an associated destruction of spongioplasm and trophoplasm, which are destroyed at the seat of the granular degeneration.

The granular disintegrations of the chromatic particles, that is, the breaking up of the aggregation of granules that form the Nissl bodies and the gradual disappearance of the individual bodies themselves, occurs even in non-nervous diseases, and is commonly attributed to pyrexia, terminal autointoxication, or local vascular lesions. In nervous disease it is usually accompanied by graver changes, such as we find in the fibrillæ.

The great majority of authorities are agreed that the fibrillar portion of the achromatic substance subserves the function of conduction of the nervous wave.

The non-organized portion of the achromatic substance is believed by Marinesco to be the seat of intense chemical phenomena, and of such importance for the nervous element as to be appropriately designated trophoplasm. That this substance is the seat of important metabolic changes is amply confirmed by other observers, especially by G. Levi, from study of fuchsinophile granules.

Golgi has stained an endocellular network which he thinks is a partial manifestation of finer and more complex structures. He has also described a reticular investment, thought by Bethe to be fibers impinging on nerve cells.

Held describes a fine meshed network which he says is not fibrils but a framework, and speaks of fine granules (neurosomes) at the nodal points of the network. These neurosomes converge at the axone hillock in lines, and in Held's pictures they have the appearance of a Cajal fibrillar structure, and might be granules lacking cement substance to form them into fibrils. In many sections stained with Cajal's method one gets the appearance of the fibrils having a granular makeup in healthy conditions, which is due to an imperfect impregnation.

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[6] Robertson, "Pathology of Mental Diseases."

The pathology of insanity has been recently discussed and has been declared insufficient. The most recent contribution is that of a case of dementia præcox,[7] which would indicate that the status of knowledge is as follows:—

"Pale yellow pigment is seen in majority of cells, central chromolysis is frequent. The cell is often swollen. The nuclei are atrophied, swollen, displaced and distorted. An endonucleolus is occasionally present. Folding of the nuclear membrane is rare. Neurophagocytosis is occasionally seen. The glia nuclei are slightly increased about the cells and occasionally cover them. Fragmentation of the cells is rare. The small pyramidal cells are frequently seen twisted upon their axes."

In the cerebellum all cells showed a granular appearance. Sections stained with Bethe's method showed the intracellular fibers distinctly stained except in the central part, where there was a granular appearance, and in some cases this involved nearly the whole cell.

The author seems to think tangential fibers are decreased in number, and that there is some increase in neuroglia tissue.

In order to advance the theory that insanity is particularly related to neurofibrils it was necessary, on account of our inability to get but two brains of insane persons at autopsy to approach it with the anatomical and physiological features bearing on the subject and the results of experiments on animals.

We found in our work at Friends' Asylum with fresh normal tissue from a rabbit by Cajal's method, large-sized cells in the medulla with fibrils running in through a process, then along the periphery of the cell, and going out by another process not necessarily an axone. Other fibrils approach nearer the nucleus and give off collaterals and continue on and out another process. Some advance directly to the nucleus, and apparently end in a network.

These features were especially noted in a large cell in the cord of a rat, where around the nucleus, there was a reticulum, while in the periphery were larger fibrillæ placed more or less parallel.—(Plate I, Fig. 1.)

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[7] Dunton, Journal of Insanity, April, 1904.

In the cortex the cells are of several sizes, some are small with a nucleus, and then a layer of fibrils around it which depart from the cell by several processes.

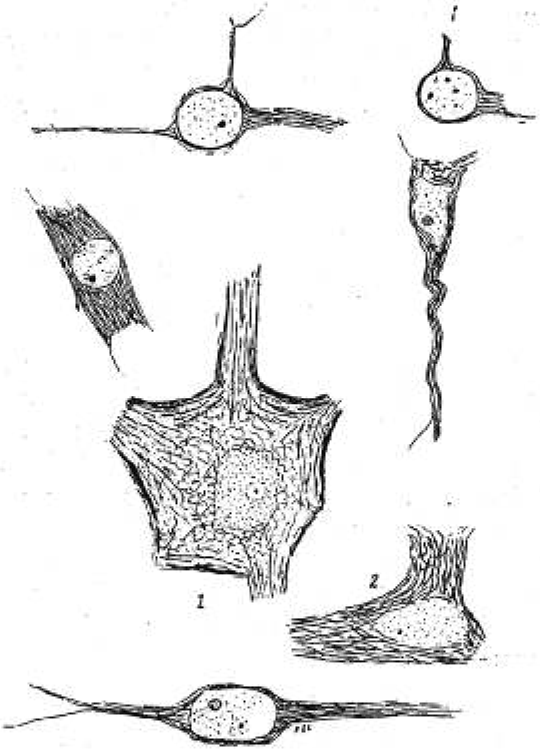

Plate I.—Normal cells from a rabbit and a rat; Cajal stain;
1. Cord of rat; 2. Medulla of rabbit.

These fibrils seem to run in one process and out another, it is difficult to see any collaterals given off. (See Plate I.)

The fibrils in the cord and medulla are larger and coarser than those in the cortex of the rabbit. In the larger sized cells in the cortex the cell body is broad, the fibers run more or less parallel, as is shown in the drawing, running from the processes at one extremity to the processes at the other. When the fibrils enter a process they are placed closer together, and give a cord-like appearance.

The nuclei in all the cells seem to be alike in many ways; there are small sized granules closely packed in some parts, leaving vacant spaces at other parts. The granules color yellow.

The nucleolus stains darker, a reddish yellow, and in it are dark granules moderately close together.

Some cells show spaces between fibrils in such an arrangement as to envelope Nissl bodies. Nissl, when speaking of bodies stained by his method and the non-staining portion, suggested the presence of fibrils in the non-staining part.

In a good stain the sections should have a reddish-brown background; if the pieces are above an eighth of an inch in size, the sections show pale centers, while the part correctly stained will be midway between that and the periphery, which is usually too dark to obtain good pictures.

In a good section the intracellular fibers take on a blackish color, but they do not stain as completely as they do in Bielschowsky's stain. The cell bodies should be a shade darker than the surrounding tissue and the fibrillæ a blackish color. The best results were obtained with a two per cent. silver nitrate solution, kept at 35 degrees C. for six days, washed in water two minutes, and then placed in one per cent. pyrogallic acid twenty-four hours, washed in water two minutes, alcohol ninety-five per cent., alcohol absolute, xylol, paraffin. Cut sections at two microns. When the sections are pale, if bathed for ten minutes in the following solution they improve:—

Amm. sulphocyanide..................	3.
Sod. hyposulphite.....................	3
Aqua	100.

Before using add a few drops of a one per cent. gold chloride solution, wash in water and clear. Many sections are not satisfactory, and it is necessary to go over a considerable number to get good ones, but when they are good they are apt to be so throughout.

In a normal brain, examined thirty-three hours after death, certain changes in the fibrils were noted, probably due to postmortem changes; differences which would not be noted in our ordinary stains. The fibrils in the majority of cells, in the region of the nucleus, had undergone granular degeneration. In the processes could be seen a few straggling fibrils intact, but these had degenerated on reaching the cell body; in some cases becoming flat and transparent. (See Plate II, Fig. 2.)

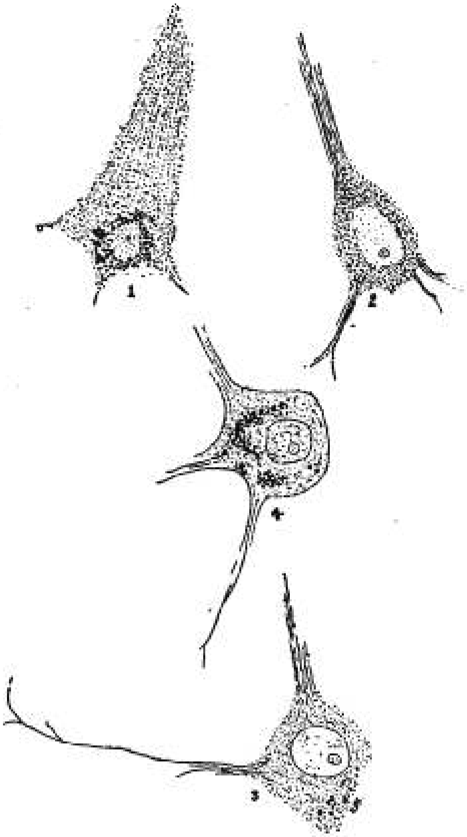

Plate. II.—Changes seen in cells in: 1. Paresis; 2. 33 hours post-mortem; 3. Starvation; 4. Insanity.

To create conditions which might simulate insanity, a rat was exhausted by starvation. His energy disappeared, and he sat in a corner of the cage perfectly still, he paid no attention to the rattling of paper or to the poking of a stick. On stirring him he seemed barely able to move. He was killed mechanically at the end of four and a half days. In the medulla were noted cells quite normal in appearance, and also cells showing distinct granular degeneration of the fibrils. At one place there were two cells side by side, one normal, and the other showing no healthy fibers at all. In the cord was a similar picking out of cells, which degenerated and a leaving of normal cells. In some cells where the fibrils show distinctly; there is a difference in their size, some being fine and interlacing, others course. In the cortex (Plate II, Fig. 3) many cells are entirely granular, often including the nucleus, which is filled with coarse granules, staining darker than the normal nuclear granulation. In the cell body are areas of a coarse black pigment. The fibrils in most of the affected cells can be demonstrated in the processes, while the cell body shows short broken pieces and fine granular lines. The nucleolus can be demonstrated, and in it a few granules, scarcely ever more than six in number.

In the second experiment an attempt was made to exhaust a rat by continuous running in a moving squirrel wheel. At the end of two and one-quarter hours the animal seemed to be quite exhausted.

Sections, however, showed only the beginning change, that is, taking the stain faintly and showing a reddish tint with some enlargement of fibrils.

In the case of insanity following we find practically the same changes as seen in the starved rat, but differing from the post-mortem change by the addition of pigment.

The case, sixty-seven years old, was one of manic-depressive type of long standing, which had developed into a very mild dementia. The patient had been able to be around, go to church, and to do sewing; she had been quite active, and had had no serious attack for five years. Sixteen days before death she became melancholic and nervous. She lay in bed, in restless motion, face pale and tense, pulse irregular and intermittent, feet and hands cold. She would lie muttering to herself and evidently in great distress, but could not be induced to speak. She paid little or no attention when spoken to, and resisted everything done for her. One morning she arose, moved a short distance, returned, and fell on the bed, dead.

Autopsy showed marked myocarditis. In this case we do not see in the brain cells the lesion of the mild dementia, but do see the cause of the acute profound depression coming on top of it. The poor circulation probably caused an anemic condition of the brain, which affected the neurofibrils, and from that, we would argue, followed the depression.

The fibrillæ are almost absent in the cell bodies, the remains can be seen often as lines of fine granules, traversing a field of fine granulation. In the cellular processes they are less affected, but are not intact, and stain less readily than the normal. Many cells contain a large amount of black pigment (Plate II, Fig. 4).

Thionin shows pigment, vacuoles and fine granulation, but no signs of fibrils at any point.

The nuclei are partially filled with corpuscular bodies, staining yellow. The nucleoli are very occasionally crumpled, but usually show from three to seven dark granules within.

The small nerve cells show similar lesions of broken fibrils and granulations.

The cord and medulla show the same changes as the cortex, which would incline one to the view of anemia as a factor in the degeneration and the primary cause of the depression.

Tissue which has been hardened in formalin gives fairly satisfactory results with one per cent hydrochinone has been used instead of one per cent pyrogallic acid.

Some pieces of cortex, so hardened from a case dying of paresis, showed the absence of fibrils in the cell body with the remnants of them in the processes; also coarse granulation in the nucleus and pigment in the cell body. (Plate II, Fig. 1).

Our studies and experiments thus far at Frankford would seem to prove the intimate relation which the neuro-fibrils of nerve cells bear to mental processes.

In the experiment of the partially exhausted rat was found the earliest change, that of swollen fibrils and inability to take the stain deeply. In the rat affected by starvation we have another phase of the etiological factor in the change of the neuro-fibrils, which plays an important part in the insanities arising from mal nutrition. We have under way other experiments to study the effects of morphia, cocaine, etc., so often a cause of insanity.

The changes quickly wrought within thirty-six hours post-mortem tend to show the delicacy of the structure of the neuro-fibrils.

The case of depression so quickly following a change in circulation which affected markedly the neuro-fibrils, would seem to indicate a close relationship between fibrils and mental manifestations. The absence of fibrils in complete paretic dementia would be what would be expected if such a relationship is true.

If we advocate an hypothesis, it is distinctly such until it is proven a fact. The establishment of relations, whether structural or functional, to be of value should be constant; and if by studying insanity pathologically, we should find these changes in a large number of cases it would then be possible to group psychoses more scientifically and to have a definite pathology of the various forms of disease. Finally, if this should prove true, undoubtedly to Cajal belongs the credit of demonstrating the method by which it can be done, and to Marinesco[8] great praise for the brilliant elucidation of his numerous experiments.

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[8] Revue Neurologique, May 15, 1904, and August 15, 1904.